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Grammatical Distinctions in the Left Frontal Cortex

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Abstract

■ Selective deficits in producing verbs relative to nouns in speech are well documented in neuropsychology and have been associated with left hemisphere frontal cortical lesions resulting from stroke and other neurological disorders. The basis for these impairments is unresolved: Do they arise because of differences in the way grammatical categories of words are organized in the brain, or because of differences in the neural representation of actions and objects? We used repetitive transcranial magnetic stimulation (rTMS) to suppress the excitability of a portion of left prefrontal cortex and to assess its role in producing nouns and verbs. In one experiment subjects generated real words; in a second, they produced pseudowords as nouns or verbs. In both experiments, response latencies increased for verbs but were unaffected for nouns following rTMS. These results demonstrate that grammatical categories have a neuroanatomical basis and that the left prefrontal cortex is selectively engaged in processing verbs as grammatical objects. ■

INTRODUCTION

Some patients with focal brain damage have difficulty naming, writing, reading, or comprehending verbs compared to nouns (Breedin, Saffran, & Schwartz, 1998; Caramazza & Hillis, 1991; McCarthy & Warrington, 1985), while others show the opposite effect (Robinson, Rossor, & Cipolotti, 1999; Bates, Chen, Tzeng, Li, & Opie, 1991; Zingeser & Berndt, 1988). These well-established patterns raise a host of questions about the ways in which information about words is represented and organized in the brain. The finding that nouns and verbs are spared and impaired differentially may suggest that the anatomy of the cerebral cortex reflects grammatical distinctions that determine how words are incorporated into phrases and sentences in speech. On the other hand, the observed dissociation may not be grammatical at all, but rather a byproduct of the kinds of meaning associated with prototypical nouns (objects) and verbs (actions). Thus words referring to actions may be represented in neural circuits that also subserve motor planning, while words for concrete objects may depend on cortical regions with connections to sensory areas (Pulvermüller, 1999; Damasio & Tranel, 1993). Here we demonstrate that grammatical categories have a neuroanatomical basis by showing that grammatical operations involving verbs can be impaired selectively with repetitive transcranial magnetic stimulation (rTMS).

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We used rTMS to target a portion of the left prefrontal cortex along the midfrontal gyrus, anterior and superior to Broca's area. Left-hemisphere frontal cortical lesions have been associated with verb production deficits in patients with a wide variety of neurological disorders, ranging from stroke (Berndt, Mitchum, Haendiges, & Sandson, 1997; Miceli, Silveri, Villa, & Caramazza, 1984) to frontotemporal dementia (Cappa et al., 1998) and neurodegenerative diseases (Bak, O'Donovan, Xuereb, Boniface, & Hodges, 2001; Daniele, Giustolisi, Silveri, Colosimo, & Gainotti, 1994). Although early reports linked impairments in verb production to more general problems with syntax and propositional speech (Luria, 1977; Myerson & Goodglass, 1972), it is not clear whether these deficits are causally related: Some patients with damage to frontal cortical regions present with sentence processing difficulties, but spared verb production (Berndt, Haendiges, & Wozniak, 1997), while other patients with lesions in various areas have difficulty producing verbs despite their fluent and grammatical speech (Berndt, Mitchum, et al., 1997; Caramazza & Hillis, 1991; Kohn, Lorch, & Pearson, 1989). Based on these data, it seems likely that some portion of the left frontal cortex, adjacent to areas involved in sentence processing, is necessary (if not sufficient) for verb retrieval.

Neuroimaging in unimpaired subjects has also been used to support the claim of a role for the left prefrontal cortex in verb processing. Electrophysiological studies have shown increased left-lateralized anterior positivity when verbs are perceived compared to nouns (Dehaene, 1995), though this effect is not present for verbs that can also be used as nouns (like *walk*) or when the sentence frame context sets up the expectation of a noun (e.g., ‘‘She liked the . . .’’; Federmeier, Segal, Lombrozo, & Kutas, 2000). Studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have shown that verb generation tasks recruit left prefrontal and medial frontal cortex—as well as a patchwork of other regions in the left temporal, parietal, and occipital lobes (Raichle et al., 1994; Wise et al., 1991; Petersen, Fox, Posner, Mintum, & Raichle, 1988, 1989). However, functional neuroimaging has so far failed to reveal anatomically distinct patterns of activation for nouns and verbs using either word generation paradigms (Warburton et al., 1996) or simpler lexical decision tasks (Fujimaki et al., 1999; Perani et al., 1999).

An advantage of rTMS is that it can be used to demonstrate not only that a brain region is active while a given task is being performed, but that the area is actually engaged in the task in question (Walsh & Rushworth, 1999). During rTMS a series of magnetic pulses is generated by a coil held against the subject's head. The resultant magnetic fields pass unattenuated through the scalp and skull, inducing a current in the underlying brain tissue (Walsh & Cowey, 2000). A train of pulses at 1 Hz frequency suppresses the excitability of the targeted region (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Pascual-Leone, Bartres-Faz, & Keenan, 1999; Chen et al., 1997), in effect creating a ‘‘virtual lesion’’ that may transiently interfere with cognitive processing beyond the duration of the train itself (Pascual-Leone, Walsh, & Rothwell, 2000).[1]

RESULTS

Experiment 1: Real Words

Our first experiment was designed to establish whether the area in question is critical for verb retrieval and not for noun retrieval. We reasoned that if this were the case, production of verbs after rTMS should be delayed relative to a baseline condition before stimulation; by contrast, rTMS should not affect the production of nouns. Word production was cued by a linguistic task in which subjects were required to produce the plural and singular forms of regular nouns (e.g., *songs*, *song*) or third-person plural and singular forms of verbs (e.g., *sing*, *sings*), with nouns and verbs presented in alternate blocks in an order that varied by subject. Performance on the blocks with rTMS was compared to performance on control blocks with sham stimulation, in which the TMS coil was positioned to produce a sensation similar to real stimulation, but no cortical interference (Figure 1).

Following sham stimulation, response latency (RT) decreased markedly from baseline for both nouns and verbs (Figure 2).[2] The magnitude of this decrease did not differ significantly between word classes when compared for individual subjects ($t(7) = 0.72$, *ns*), and an analysis of variance (ANOVA) on RT by subjects reveals a marginal main effect of time relative to stimulation ($F(1,7) = 4.19$, $p < .08$) but no interaction between time relative to stimulation and grammatical class ($F(1,7) = 0.53$, *ns*). Real stimulation produced a delay relative to baseline only in verb production ($t(7) = 2.03$, $p < .05$); RT for nouns declined just as it did after sham stimulation ($t(7) = 0.81$, *ns*). An ANOVA by subjects after real stimulation shows a robust interaction between time relative to stimulation and grammatical class ($F(1,7) = 9.72$, $p < .02$). This finding indicates that rTMS applied to left frontal cortex differentially affects the processing of nouns and verbs, specifically hindering verb production. However, these results do not reveal what kind of information about verbs is represented in the left prefrontal cortex: Is it semantic, that is, related to meaning, or is it purely grammatical?

Given that the list of verbs used as stimuli in the first experiment included not only actions but also more abstract relations like *lose* and *please*, it seems unlikely that the verb-specific disruption observed following

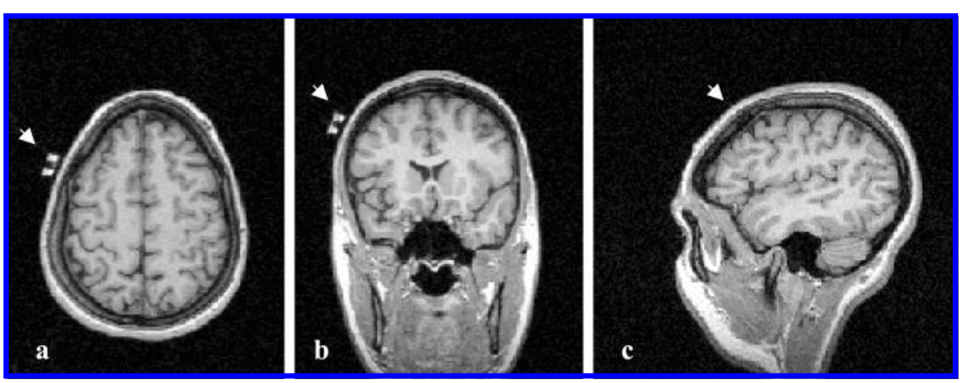

Figure 1. (a) Axial, (b) coronal, and (c) sagittal MRI scans indicating the position of the TMS coil for a representative subject.

rTMS can be attributed to the suppression of motor planning functions. (Many of the nouns were also abstract, e.g., *choice* and *debt*.) It is nonetheless possible that circuits in the left prefrontal cortex encode other types of semantic information about verbs, such as the various thematic relations they specify between people and things (e.g., "who does what to whom"; Gentner, 1981).

Experiment 2: Pseudowords

To address this question we performed a second experiment, identical to the first except that the noun and verb stimuli were replaced with phonologically and orthographically plausible one-syllable pseudowords such as *wug*, *cheen*, and *flonk*. Pseudowords obviously have no stored representations, semantic or otherwise; they can be interpreted, if at all, only by vague association with known words. Treating a pseudoword as a grammatical object, on the other hand, is intuitively straightforward as long as one knows the putative grammatical class of the pseudoword in question. Moreover, the same pseudowords can be presented as nouns and verbs, controlling for any possible differences in the ease with which subjects retrieve and articulate the sounds of the words to be produced in each condition. At least one study has shown that a patient with a grammatical class-specific deficit, in this case for nouns, also has trouble producing the appropriate forms of pseudonouns (Shapiro, Shelton, & Caramazza, 2000).

If the left prefrontal cortex is crucial for the representation of information relating to verb meaning, but plays no role in category-specific grammatical operations, we should not expect to find that suppression of this area with rTMS results in a selective delay in the

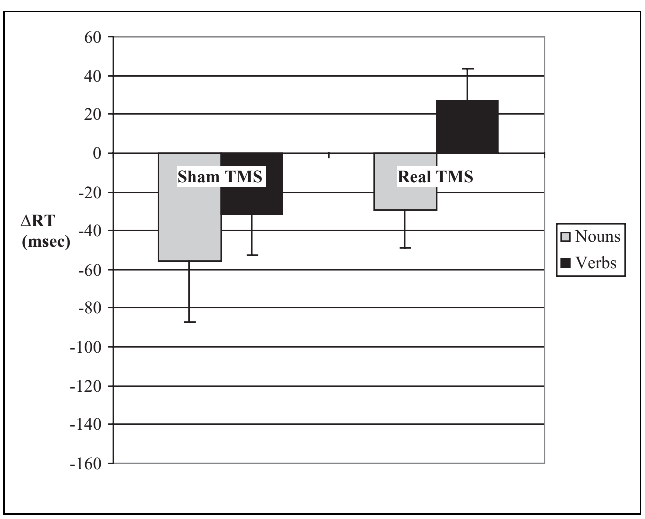

Figure 2. Effects of rTMS on production of real nouns and verbs. Following sham stimulation, average response latencies (RT) decreased markedly from baseline for both nouns and verbs.

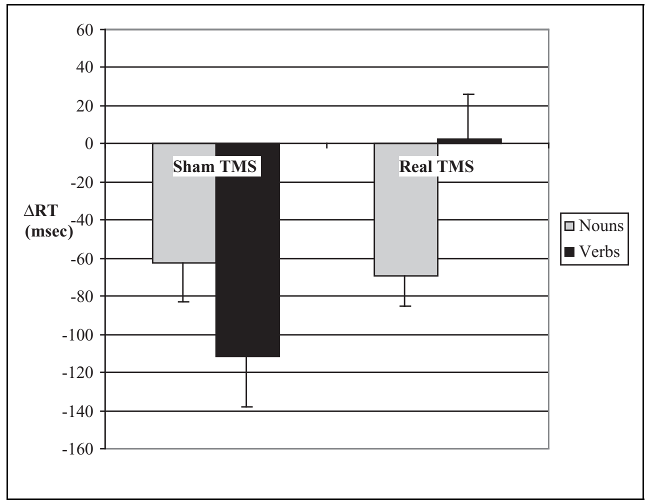

Figure 3. Effects of rTMS on production of pseudowords used as nouns and verbs. As with real words, statistically equivalent decreases in average response latency were observed after sham stimulation for both nouns and verbs.

production of pseudoverbs compared to (phonologically identical) pseudonouns. By contrast, if this area mediates retrieval of grammatical information about verbs, production of pseudoverbs should be impaired in the same manner as production of real verbs. In fact, the latter is what we observed (Figure 3).[3] As with real words, statistically equivalent decreases in average response latency were observed after sham stimulation for both nouns and verbs [$t(5) = 1.57$, *ns*]; in an ANOVA by subject there was a large main effect of time relative to stimulation [$F(1,5) = 24.5$, $p < .005$] and no interaction between this variable and grammatical class [$F(1,5) = 2.47$, *ns*]. Real stimulation produced a decrease in RT for nouns nearly identical to the sham condition but a slight delay in verb production that differs substantially from the change in RT after sham stimulation [$t(5) = 5.29$, $p < .004$]. In the real stimulation condition there was again a strong interaction between grammatical class and time relative to stimulation [$F(1,5) = 19.2$, $p < .01$].

DISCUSSION

rTMS Abolishes the Practice Effect for Verbs, but not Nouns

It is well known that the repetition of tasks involving verbal production of a limited number of stimuli effects a substantial decrease in response latency over time. Our findings indicate that rTMS applied to the anterior portion of the left midfrontal gyrus blocks this natural practice effect for pseudowords used as verbs, and reverses it for real verbs.

Before concluding that suppression of the left prefrontal cortex selectively hinders retrieval of words belonging to the grammatical category of verbs, we should consider the possibility that this pattern may arise partly or even largely as a result of uncontrolled disparities in the difficulty of producing different target words. For example, some researchers have suggested that normal subjects are slower at processing verbs than nouns under certain experimental conditions (Reyna, 1987). If it is true that some of the words we used are in general more difficult to produce than others (reflected by larger response latencies), applying rTMS may simply have made ''hard'' words even harder to produce, or caused them to benefit less from practice, irrespective of grammatical class.

Our analysis showed that rTMS did not interfere more with words within a class that take longer to produce before stimulation, suggesting that a simple effect of difficulty cannot explain the different patterns of change in mean reaction time observed between classes.[4] Thus, while it is possible that the effects of rTMS on word production may be modulated by any of several psycholinguistic variables apart from grammatical category, it nevertheless appears that trains applied over a portion of the left midfrontal gyrus have a disproportionately large impact on the retrieval of information relating to the grammatical role of verbs. This is consistent with reports of verb deficits associated with left frontal lesions in aphasic patients, as we have noted, as well as with observations from electrophysiological and neuroimaging studies of brain activity during word production.

The Left Prefrontal Cortex is Engaged in Verb Processing

Two important conclusions follow from these results. First, these data demonstrate that the left prefrontal cortex is involved in the process of verb retrieval, but is not critical for noun retrieval.[5] Second, we have shown that this region subserves processing of grammatical information about verbs. This result is clearly in disagreement with proposals that the left frontal cortex encodes action words, but not verbs as such. At the same time, it accords well with neuroimaging studies which show that portions of the left frontal lobe are active while subjects are retrieving verbs. In at least one PET study, activation of left frontal cortex during action word generation was attributed specifically (though without any direct motivation) to the recruitment of areas involved in processing grammatical properties of verbs (Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995).

Our observations are also consistent with findings from electrophysiology, which indicate that anterior positivity is greatest when an unambiguous verb is presented in an appropriate sentence context, but disappears when verbs are presented in a context that sets up the expectation of a noun. These studies also show that left frontal positivity is not observed in response to grammatically ambiguous words with motor associations (Federmeier et al., 2000), contrary to what we would expect if this part of the brain were involved in representing semantic information about actions.[6]

The notion that grammatical knowledge may have a neuroanatomical and functional basis separate from other aspects of a word's representation is attractive in light of psycholinguistic models of sentence production which postulate that the ordering of words in a syntactic frame takes place separately from the retrieval of the same words' meanings (semantics) and sound structures (phonology) (e.g., Garrett, 1980). Hence, slips of the tongue and misordering errors tend to respect syntactic categories: That is, people replace nouns with nouns and verbs with verbs (as in the erroneous phrase ''a laboratory in our own computer'') (Fromkin, 1971).

Returning to neuropsychology, the autonomy of grammatical and semantic knowledge is important in accounting for certain puzzling phenomena that arise in connection with verb-specific deficits, such as the observation that many patients can produce novel grammatical verbs like ''laddering'' when they are unable to access appropriate action names (in this case, *climbing*) (Shapiro & Caramazza, in press; McCarthy & Warrington, 1985). Oftentimes, such patients present with more posterior (fronto-temporal or fronto-parietal) lesions, with no specific evidence of prefrontal damage (Silveri & di Betta, 1997). (In this connection it is worth noting again that PET and fMRI studies of verb generation show recruitment of several left-hemisphere regions aside from the frontal lobe.) Still other patients can produce verbs to name pictures of actions despite massive frontal lesions (De Renzi & di Pellegrino, 1995; Bates et al., 1991), implying that the semantic and phonological forms of verbs are accessible. Such observations suggest that verbs (and other words) are represented in distributed cortical networks, with semantic, phonological, and grammatical features occupying distinct patches of neural tissue that can be damaged independently of one another.

Why might the left prefrontal cortex be involved in the representation of the grammatical category of verbs? One possibility is that the correlation between verbs and actions, while not sufficient to explain verb production deficits in patients with focal brain damage, is nevertheless critical for establishing the neural localization of categorical knowledge about verbs during the process of language acquisition (Caramazza, 1994). The ''semantic bootstrapping'' hypothesis holds that a child uses the close relations between the semantically definable classes ''concrete object'' and ''action'' on the one hand, and nouns and verbs on the other, to sort out the basic rules of word order (phrase structure) in syntax. Once phrase structure rules have been established, the child can relax the syntactic–semantic correspondence to include semantically nonprototypical instances of nouns and verbs (Pinker, 1984). On this hypothesis, the initial categorization of actions as verbs may serve to localize verb-specific syntactic information in cortical regions adjacent to motor planning areas.

CONCLUSION

Word production is a multistage process with separate components involved in the computation of a word's meaning, grammatical function, and sound structure; nouns and verbs may differ prototypically in any or all of these dimensions. Our findings suggest that with respect to at least one dimension, grammatical category, nouns and verbs have distinct neuroanatomical underpinnings, and can be dissociated by targeted suppression of the left prefrontal cortex. Other aspects of noun and verb representations are likely to be subserved by distributed networks of neural regions in the left hemisphere, though at present neither the spatial configuration nor the functional architecture of these networks is well understood. Future investigations will no doubt contribute to mapping the neural correlates of knowledge about words.

METHODS

Participants

Eight right-handed native speakers of English (4 males and 4 females) aged 20 to 29 years (mean = 21.6 years) participated in the first experiment. Six right-handed native speakers of English (1 male and 5 females) aged 18 to 21 years (mean = 19.5 years) participated in the second experiment. All subjects were healthy, with no history of neurological or psychiatric illness, and all were naïve to TMS before taking part in the study.

Application of rTMS

We applied rTMS using a Magstim Rapid Rate stimulator (Magstim, Whitland, UK) and a focal 8-shaped coil with wings measuring 43 mm in diameter. These devices were used under an investigational device exemption from the Food and Drug Administration. The current induced in the brain was around 10–15 mA/cm^2, the peak magnetic field strength was approximately 3.5 T and the peak electric field was 660 V/m (Barker, Freeston, Jalinous, & Jarratt, 1987). During the experiment, subjects sat comfortably in a reclining chair. For each subject we first identified the optimal scalp location for induction of motor-evoked potentials in the contralateral abductor pollicis brevis muscle. Single pulse TMS was then applied at decreasing intensities to determine motor threshold, following guidelines established by the International Federation of Clinical Neurophysiology.

The scalp position for stimulation in each subject was 6 cm anterior and 1 cm ventral to the motor spot for the first dorsal interosseous muscle, targeting an inferior portion of the midfrontal gyrus just anterior and superior to Broca's area. This position was marked on tightly fitting Lycra caps worn by the subjects, whose heads were held in place with chin and forehead rests. Repetitive TMS was applied at 110% of motor threshold intensity and 1 Hz frequency as a single train of 300 sec duration; the coil's position was maintained using an articulated arm and clamps. An anatomical brain MRI was obtained to identify the brain area targeted by TMS. The focality of the brain effects of TMS depend on coil geometry; the small 8-shaped coil employed in the present experiment affects functionally small volumes of cortex with a specificity similar to PET or fMRI (Jalinous, 1991). Information about depth penetrance, spatial resolution, and specific neural elements affected by TMS is limited. For the purposes of the present experiment, however, functional resolution is the critical variable (Mottaghy et al., in press; Kosslyn et al., 1999; Siebner et al., 1998; Chen et al., 1997).

Real rTMS was applied with the stimulation coil resting tangentially on the subject's scalp and the handle pointing posteriorly parallel to the subject's midsagittal plane. Sham rTMS was applied with the coil angled 90° away from the subject's scalp and resting on the edge of a single wing. This form of stimulation has been shown not to induce a significant current in a subject's brain while generating similar percepts. Our subjects were naïve to rTMS and were unable to distinguish sham from real rTMS. Nevertheless, all underwent sham rTMS first, followed by real rTMS.

Experimental Task

The task was performed on a Macintosh computer using PsychLab™ and a CMU button box with voice key to record responses. Before beginning the task, the subject fixated on a crosshair at the center of the computer screen, and was instructed to press the space bar in order to move on to the first trial. Following every trial, the fixation point reappeared and the subject was required to press the space bar to proceed.

In each trial the subject was presented with a written stimulus word (either a noun or a verb) which appeared in the position of the fixation point for 250 msec, followed for another 250 msec by a symbolic cue indicating the morphological form in which the word was to be produced aloud—singular (✧) or plural (✧✧✧) for nouns, third-person singular (△) or plural (△△△) for verbs. The subject's response latency to generate the appropriate form was recorded by voice key. Note that the grammatical operations involved in producing these words have identical phonological consequences: That is, for both nouns and verbs the task called for adding or deleting the morpheme /z/ (written as final *s* and realized phonetically as [z], [s], or [ɪz], depending on the final consonant of the stem). Plural and singular stimulus words were paired randomly with cues so that the required manipulation (if any) for each stimulus was unpredictable. Nouns and verbs were all one syllable in length and real words were matched as closely as possible for phonology and frequency (Kucera & Francis, 1982).

The experiment was divided into 4 blocks, each of which consisted of 2 sets of 80 trials separated by an interval of 300 pulses of rTMS. A single list of 40 words (or pseudowords) was used twice in each set, such that each of the 4 possible stimulus–cue pairings for a given word (singular target–singular cue, singular target–plural cue, etc.) was encountered once within a block. A 10-min rest period followed each block to allow the effects of rTMS to wash out. Though the morphological cues differed by word class, subjects were also told prior to each block whether the words in that block would be nouns or verbs. The order of presentation of noun and verb blocks was counterbalanced across subjects.

Data Analysis

Reaction times were excluded from the data set if the subject responded incorrectly, self-corrected, hesitated, or pressed the space bar before the fixation point reappeared on the screen, or if they fell outside the arbitrary range of 200–1700 msec. Using these criteria, 5.2% of the total number of responses to real words and 7.5% of the total number of responses to pseudowords were counted as errors. Subjects made significantly more errors with pseudowords than with real words ($p < .001$).

Acknowledgments

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Notes

1. The exact duration of the effects of such an rTMS train is unclear. Studies in motor cortex (Chen et al., 1997), visual cortex (Boroojerdi, Prager, Müllbacher, & Cohen, 2000; Kosslyn et al., 1999), cerebellum (Theoret et al., unpublished data), and prefrontal cortex during a working memory task (Mottaghy, Gangitano, Sparing, Krause, & Pascual-Leone, in press) suggest that the effects after the end of the train last for at least half the time of the train duration itself.
2. RT for nouns was 553 msec before and 498 msec after sham stimulation, 501 msec before and 471 msec after real stimulation; for verbs, mean RT was 633 msec before and 601 msec after sham stimulation, 559 msec before and 586 msec after real stimulation.
3. Mean RT for pseudonouns was 529 msec before and 467 msec after sham stimulation, 504 msec before and 432 msec after real stimulation; for pseudoverbs, mean RT was 663 msec before and 551 msec after sham stimulation, 525 msec before and 527 msec after real stimulation.
4. We analyzed the correlation between baseline reaction time (an average of response latencies for a given word in the presham, postsham, and prereal stimulation conditions) and the amount of interference (∂RT) observed for a given word following real rTMS. The difficulty hypothesis predicts that this correlation should be positive for nouns and verbs; that is, that stimulation should interfere more with words that are more difficult to produce. In fact, we found that the correlation between baseline RT and ∂RT for real nouns and verbs as well as for pseudonouns and verbs was negative in each case, indicating that rTMS interfered less with harder words than with easier words within a category. Moreover, there was no difference between the correlation coefficients for real nouns [$r(80) = -.22$] and verbs [$r(80) = -.19$, $t(156) = -0.30$, *ns*], or between the coefficients for pseudonouns [$r(80) = -.32$] and pseudoverbs [$r(80) = -.29$, $t(156) = 0.59$, *ns*]. This suggests that the difficulty effect is a within-category phenomenon, and that the differences in mean RT before and after stimulation for each category are due to the interaction of stimulation with grammatical class.
5. An important question is whether the left prefrontal cortex is involved directly in verb production or whether the disruption in word retrieval observed following rTMS results from altered activity in other cortical regions with connections to this area. Given that rTMS was applied over a period of 300 sec, it is at least possible that stimulation induced transsynaptic modification in distant neural circuits. We believe that the convergence between the data reported here and the results of other neuroimaging studies and lesion studies in brain-damaged patients implies a direct role for left prefrontal regions, though we note that even if this were not the case the findings we report nevertheless suggest that nouns and verbs have distinct neuroanatomical correlates. The issue remains open to further investigation.
6. Federmeier et al. (2000) have also noted that the P200 response for verbs reported by Preissl, Pulvermüller, Lutzenberger, and Birbaumer (1995) was observed in response to nonaction words as well as action words. This contradicts the suggestion that the P200 response reflects a word's semantic associations with motor activity (Pulvermüller, 1999).

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